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Abstract

Pharmacological Properties of Linearolactone against the Amoebiasis Caused by *Entamoeba histolytica*: An *In-Silico* Study †

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Abstract: Linearolactone (LL) isolated from *Salvia polystachya* presents antiparasitic activity against *E. histolytica* and *G. lamblia* through ROS production, an apoptosis-like process, and alteration of the actin cytoskeleton. However, the possible toxicological effects or molecular mechanisms of LL are still not understood. The aim of this study was to determine the pharmacological and toxicological properties of LL by bioinformatic analyzes. The pharmacological activities, toxicological risks, and molecular targets of LL were determinate by free software such as Molsoft©, Molinspiration©, ToxiM©, SuperCYPsPred©, and SEA©. Molecular docking with key proteins for the pathogenic activity of *E. histolytica* trophozoites, such as myosin-II and calreticulin, was performed with AutoDock-Vina and UCSF-Chimera. Results revealed that LL present drug-likeness of -0.55 and ToxiM of 0.958 due to medium toxicity associated with interactions in nuclear receptors (0.66), GPCR ligands (0.65), and enzymatic inhibitions (0.47) related to the cytochrome-P450 system (CYP3A4, low). Results indicate that LL is a hydrophobic molecule (*LogP*: 1.59) with intermediate intestinal absorption (*TPSA*: 65.75, CACO-2 permeability) and medium blood-brain barrier penetration (3.86). SEA analysis demonstrated that the potential target pharmacophores are OPRK1 (*P*-Value: 6.49 $x10^{-37}$, Max TC: 0.49) and NLRP3 (*P*-Value: 3.90 $x10^{-19}$, Max TC: 0.36) in humans. Molecular docking of LL with *E. histolytica* proteins showed high affinity to ATP-binding catalytic site in heavy-chain (GLU-187.A, THR-186.A, ASN-234.B) of myosin-II (-8.30 Kcal/mol), as well as in the chain-A and C (LYS-199.A, LYS-152.C) of calreticulin (-8.77 Kcal/mol). As conclusions, LL is a compound with possible moderate toxicity, sedative effects on CNS, and anti-inflammatory properties. In addition, LL probably inhibits amoebic liver abscess formation through interactions with myosin-II and calreticulin from *E. histolytica*, but in-depth studies are necessary to confirm these claims.

Keywords: Linearolactone; Pharmacological properties; Toxicological effects; *Entamoeba histolytica*; *In-silico* analysis